

### **REMARKS/ARGUMENTS**

#### THE INVENTION.

This invention provides for an efficient and economic means to differentially diagnose prostate cancer from benign prostate hyperplasia (BPH) by looking at differences in low molecular protein markers using mass spectroscopy.

#### STATUS OF THE CLAIMS.

Claims 1, 8, 12, 20, and 84-94 are pending. Claim 1 is amended to limit the sample to seminal fluids. Support for seminal fluid is found in original claim 8. Claim 8 is dependent upon claim 1 and has been amended to delete non-seminal fluid samples.

The pending claims are rejected under §112 first and second paragraphs and are provisionally rejected for double patenting.

#### REJECTIONS UNDER §112

The Examiner has rejected the pending claims as unduly broad. He properly states that the law requires that the claim scope must correspond to the teachings of the specification and that practice of the invention must not require undue experimentation. The Examiner's specific concerns are several. To fully respond, applicants view the Examiner's concerns as including three primary concerns that are specific to the claimed assay and several secondary concerns that are of a general nature and applicable to any diagnostic assay.

The primary issues concern the fact that the claim relies on a single patient sample, that applicants have not demonstrated the invention works with samples beyond seminal fluids, and that different MS probe surfaces might provide different results. Secondary concerns raised by the Examiner rely upon background publications reminding readers that protein fingerprinting-based MS assays suffer from a host of potential problems including machine sensitivity, reproducibility, sample handling, and the manner and timing of sample acquisition from the patient.

Applicants have responded to the Examiner's remaining issues by amending the claims and with a Rule 132 by a co-inventor, Dr. Tai-Tung Yip.

The Examiner raised a concern that the observation of a low molecular weight shift in protein markers between patients with prostate cancer and benign prostate hyperplasia might be restricted to the specific chemistry used to adsorb the proteins to the MS probe. Dr. Yip provides evidence in his declaration that the claimed observation was demonstrated using two additional surface chemistries.

The Examiner observed that the initial work was done with a sample from a single patient and raised a concern that the invention might not be reproducible across a larger patient population. Dr. Yip uses his Rule 132 Declaration to provide the Examiner with a copy of two published papers, Adam *et al.* (2002) Cancer Research 62:3609-3614 and Cazares *et al.* (2002) Clinical Cancer Research 8:2541-2552. In the Adam paper, co-inventor George Wright reports on his follow-up work with hundreds of serum samples. In Cazares, the same group reports on results using prostate tissue samples. Dr. Yip explains in his declaration that these 2002 papers provide ample evidence that prostate cancer patients have a significant increase in lower molecular weight proteins in their serum- and prostate-related tissues and fluids compared to patients with benign prostate hyperplasia, also called benign prostate syndrome (BPS).

The Examiner's final concern relating specifically to the prostate cancer assay was the fact that the examples all used seminal fluid and the claims read on other fluids and tissue samples. In response, applicants have amended the claims to recite the body samples from which they can provide actual evidence of the invention working.

A number of secondary issues were raised by the Examiner who relied on concerns raised in the Grizzle and Diamondis papers concerning the use of mass spectroscopy to provide reliable diagnostic assays based on protein profiling or fingerprinting. The concerns were several, but they all related to general concerns applicable to any diagnostic assay. Among the concerns raised by the authors were instrument variations, sample handling, the containers used to hold the

samples, controlling for patient variables such as diet, stage of disease and patient condition, loss of markers due to binding of small proteins to larger more abundant proteins and the like.

In his Rule 132 declaration, Dr. Yip explains that these secondary issues are applicable not only to the claimed assay, but to any MS-based assay looking at protein fingerprinting for diagnostic purposes. Dr. Yip goes on to explain that most, if not all, of these variables are routinely avoided by those of skill. For example, a well maintained mass spectroscope is critical for the practice of the invention. Any environmental conditions that might result in the degradation or contamination of the proteins in a sample are important to avoid if one plans to look at protein fingerprinting.

As explained by Dr. Yip, the secondary concerns are generally applicable to any protein based assay. It is similar to a PCR-based diagnostic assay where it is important to avoid conditions that denature the polymerases or degrade the target nucleic acid. So long as the concerns are avoided by good laboratory practices that are routinely practiced by those of skill, patent applicants should not have to address such issues to establish that their assays are enabled. For example, there is no evidence that those of skill would need to be taught to avoid repetitive freeze/thawing cycles of a protein sample being stored for fingerprinting, or that those of skill would need a specific teaching to avoid plastic containers that might leach chemicals into the samples.

As final evidence that MS protein-based fingerprinting has become widely accepted as an appropriate basis for diagnostic assays, applicants have attached a recent press release from CIPHERGEN (Exhibit A). The press release details their recent success in a multi-center validation study with a diagnostic assay for detecting ovarian cancer using protein fingerprinting.

Unless the Examiner has specific reasons to believe that the secondary concerns raised by Gizzle *et al.* and Diamandis are not routinely controlled for by good laboratory practices, the secondary issues cannot be used to support an enablement rejection. For if routine laboratory practices avoid the secondary concerns, they cannot be said that the claims require undue experimentation to practice the invention within their full scope.

In view of the amendment to the claims, Dr. Yip's Rule 132 Declaration, the exhibits and the arguments set forth above, applicants believe that they have fully addressed the outstanding concerns raised by the Examiner under §112.

#### PROVISIONAL DOUBLE PATENTING REJECTION

Finally, there is a provisional double patenting rejection over co-pending applications No.10/221,905, 10/513,649 and 10/505,367. Applicants acknowledge the rejection and believe that the subject application will be the first to issue. Accordingly, applicants reserve the right to file a terminal disclaimer at the appropriate time during prosecution of the '905 application. Applicants believe that no further response is required (see MPEP 804 IB "Between Copending Applications - Provisional Rejections").

#### CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

Applicants believe that no fee is required for submission of this response. However if a fee is required, the Commissioner is authorized to deduct such a fee from the undersigned's Deposit Account No. 20-1430. Please deduct any additional fees from or credit any overpayment to, the above noted Deposit Account.

Appl. No. 10/088,970  
Amdt. dated June 26, 2006  
Reply to Office Action of March 24, 2006

PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

/Kenneth A. Weber/

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KAW/jhd

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Source: CIPHERGEN BIOSYSTEMS, INC.

## CIPHERGEN REPORTS POSITIVE RESULTS FROM MULTI-CENTER VALIDATION OVARIAN CANCER BIOMARKER STUDY

Monday June 5, 9:00 am ET

### Results Presented at the Annual Meeting of the American Society of Clinical Oncology

FREMONT, Calif., June 5 /PRNewswire-FirstCall/ -- CIPHERGEN Biosystems, Inc. (Nasdaq: CIPH - [News](#)) announced today results of a multi-center study evaluating the performance of a set of seven biomarkers for the detection of ovarian cancer. 607 patient samples taken from five international medical centers were evaluated for each of the seven markers. 234 women had benign gynecologic disease and 373 patients had invasive epithelial ovarian cancer, including 101 with early stage cancer. All seven biomarkers individually demonstrated statistically significant power to differentiate ovarian cancer patients from women with benign disease, and most biomarkers had  $p < 0.0001$ . As in previous studies, an index derived from the seven markers demonstrated improved specificity for discriminating ovarian cancer from benign pelvic masses, as well as for the detection of early stage cancer. This is the first time that biomarkers discovered through current clinical proteomics efforts have been subjected to a large-scale multi-institutional independent validation study.

The Johns Hopkins Medical Institutions; University of Texas MD Anderson Cancer Center; University Hospitals, Leuven, Belgium; Rigshospitalet, University of Copenhagen Hospital, Copenhagen, Denmark; University of Kentucky; and Groningen University Medical Center, Groningen, The Netherlands participated in the study. The paper was presented by Dr. Zhen Zhang, Associate Professor, Department of Pathology, The Johns Hopkins University School of Medicine.

"We are very pleased with the results of this study. Demonstrating the multi-center validity of our markers is a key milestone in the development of a test that can aid in distinguishing women with ovarian cancer from women with benign ovarian tumors," said Gail S. Page, President and CEO. "We have now shown the utility of these markers in large multi-institutional retrospective studies as well as in prospective studies."

The particular study presented at the ASCO Annual Meeting is part of a comprehensive ovarian cancer program being conducted by CIPHERGEN in conjunction with leading collaborators at The Johns Hopkins School of Medicine, the University of Texas M.D. Anderson Cancer Center, University College London, and the University of Kentucky. In addition to the ongoing work aimed at developing assays that are designed to distinguish between benign and malignant pelvic mass, CIPHERGEN has studies underway to target the prediction of recurrence of ovarian cancer as well as to provide additional tools to aid the physician in triaging women considered at high risk of ovarian cancer.

#### About CIPHERGEN

CIPHERGEN is dedicated to the discovery of protein biomarkers and panels of biomarkers and their development into protein molecular diagnostic tests that improve patient care; and to providing collaborative R&D services through its Biomarker Discovery Center® laboratories for biomarker discovery for new diagnostic tests as well as pharmacoproteomic services for improved drug toxicology, efficacy and theranostic assays. CIPHERGEN develops, manufactures and markets a family of ProteinChip® Systems and services for clinical, research and process proteomics applications. ProteinChip Systems enable protein discovery, validation, identification and assay development to provide researchers with predictive, multi-marker assay capabilities and a better understanding of biological function at the protein level. Additional information about CIPHERGEN can be found at [www.ciphergen.com](http://www.ciphergen.com).

## EXHIBIT A

#### Safe Harbor Statement

**Note Regarding Forward-Looking Statements:** For purposes of the Private Securities Litigation Reform Act of 1995 (the "Act"), Ciphergen disclaims any intent or obligation to update these forward-looking statements, and claims the protection of the Safe Harbor for forward-looking statements contained in the Act. Examples of such forward-looking statements include statements regarding the predictive value and usefulness of the reported multi-marker panel in helping triage women being evaluated with a persistent pelvic mass or pelvic pain, the impact on patient outcome of patient referrals to a specialist gynecologist, the potential outcome of studies designed to predict recurrence of ovarian cancer and/or to act as a tool to aid a physician in triaging women considered at high risk of ovarian cancer, and the ability of Ciphergen to create diagnostic tests to aid physicians in predicting recurrence of ovarian cancer and/or triaging women considered at high risk of ovarian cancer. Actual results may differ materially from those projected in such forward-looking statements due to various factors, including the fact that the performance of this or any other multi-marker panel discovered by Ciphergen may not validate in subsequent studies or be developed into an assay that is useful to physicians and patients. Investors should consult Ciphergen's filings with the Securities and Exchange Commission, including its Form 10-K dated March 17, 2006, for further information regarding these and other risks of the Company's business.

**NOTE:** Ciphergen, ProteinChip, Biomarker Discovery Center are registered trademarks of Ciphergen Biosystems, Inc.

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